The paragraph presented above incorporates changes as indicated by the marked-up version below.

Various fragments of the mouse *Shh* gene were cloned into the pET11D vector as fusion proteins with a poly(His) leader sequence to facilitate purification. Briefly, fusion genes encoding the mature M-*Shh* protein (corresponding to Cys-25 through Ser-437 of SEQ ID No. 11) or N-terminal containing fragments, and an N-terminal exogenous leader having the sequence M-G-S-S-H-H-H-H-H-H-L-V-P-R-G-S-H-M (SEQ ID No. 47) were cloned in pET11D and introduced into *E. coli*. The poly(His)-*Shh* fusion proteins were purified using nickel chelate chromatography according to the vendor's instructions (Qiagen catalog 30210), and the poly(His) leader cleaved from the purified proteins by treatment with thrombin.

In the claims:

For the convenience of the Examiner, all claims being examined, whether or not amended, are presented below.

Please cancel claims 3, 4, 15, and 16 without prejudice.

1. (**Thrice Amended**) A method for promoting growth, differentiation, or survival of a cell comprising contacting said cell with an amount of a *hedgehog* polypeptide that binds to a naturally occurring *patched* receptor, which polypeptide is encoded by a nucleic acid that hybridizes under stringent conditions, including a wash step of 0.2 x SSC at 65 °C or higher stringency, to a nucleic acid sequence selected from SEQ ID No: 1, SEQ ID No: 2, SEQ ID No: 3, SEQ ID No: 4, SEQ ID No: 5, SEQ ID No: 6 and SEQ ID No: 7, wherein said amount is effective to promote growth, differentiation, or survival of the cell.

2. (**Thrice Amended**) A method for promoting one or more of growth, differentiation, or survival of a mammalian cell responsive to *hedgehog* induction, comprising treating the cell with an amount of a *hedgehog* polypeptide that binds to a naturally occurring *patched* receptor, thereby altering, relative to the cell in the absence of *hedgehog* treatment, at least one of (i) rate of growth, (ii) differentiation, or (iii) survival of the cell, said *hedgehog* polypeptide being

encoded by a nucleic acid that hybridizes under stringent conditions, including a wash step of 0.2 x SSC at 65 °C or higher stringency, to a nucleic acid sequence selected from SEQ ID No: 1, SEQ ID No: 2, SEQ ID No: 3, SEQ ID No: 4, SEQ ID No: 5, SEQ ID No: 6 and SEQ ID No: 7, wherein said amount is effective to promote growth, differentiation, or survival of the cell.

5. **(Amended)** The method of claim 2, which polypeptide comprises an amino acid sequence designated in one of SEQ ID No: 8, SEQ ID No: 9, SEQ ID No: 10, SEQ ID No: 12, SEQ ID No: 13 or SEQ ID No: 14, or an N-terminal fragment thereof that binds to a naturally occurring *patched* receptor.

6. **(Amended)** The method of claim 5, wherein said fragment comprises an extracellular fragment of at least 50 amino acids.

7. **(Amended)** The method of claim 2, which polypeptide comprises an amino acid sequence designated in SEQ ID No: 34, or an N-terminal fragment thereof that binds to a naturally occurring *patched* receptor.

11. **(Reiterated)** The method of claim 2, wherein the polypeptide modulates the differentiation of neuronal cells.

12. **(Amended)** The method of claim 11, which neuronal cells are selected from motor neurons, cholinergic neurons, dopaminergic neurons, serotonergic neurons, and peptidergic neurons.

13. **(Reiterated)** The method of claim 11, wherein the polypeptide promotes survival of the neuronal cells.

14. **(Amended)** A method for promoting, in an animal, cell growth, cell differentiation or cell survival, comprising administering an amount of a polypeptide including a *hedgehog* amino acid sequence at least 80% identical to an amino acid sequence designated in one of SEQ ID No: 8, SEQ ID No: 9, SEQ ID No: 10, SEQ ID No: 11, SEQ ID No: 12, SEQ ID No: 13, SEQ No: 14, SEQ ID No: 34, SEQ ID No: 40, SEQ ID No: 41, or an N-terminal fragment of any preceding

sequence that binds to a naturally occurring *patched* receptor, to alter, relative to the absence of treatment, at least one of (i) rat of growth, (ii) differentiation, or (iii) survival of one or more cell types in the animal, wherein said polypeptide does not originate from drosophila, and wherein said amount is effective to promote cell growth, cell differentiation, or cell survival in the animal.

17. **(Amended)** A method of claim 14, which polypeptide comprises an amino acid sequence designated in one of SEQ ID No: 8, SEQ ID No: 9, SEQ ID No: 10, SEQ ID No: 11, SEQ ID No: 12, SEQ ID No: 13, SEQ No: 14, SEQ ID No: 34, SEQ ID No: 40, SEQ ID No: 41, or an N-terminal fragment thereof that binds to a naturally occurring *patched* receptor.

18. **(Amended)** The method of claim 17, wherein said fragment comprises an extracellular fragment of at least 50 amino acids.

22. **(Reiterated)** The method of claim 14, which method modulates differentiation of neuronal cells in the animal.

23. **(Amended)** A method for inducing a cell to differentiate to a neuronal cell phenotype, comprising contacting said cell with a polypeptide including a *hedgehog* amino acid sequence at least 80% identical to an amino acid sequence designated in at least one of SEQ ID No: 8, SEQ ID No: 9, SEQ ID No: 10, SEQ ID No: 11, SEQ ID No: 12, SEQ ID No: 13, SEQ No: 14, SEQ ID No: 34, SEQ ID No: 40, SEQ ID No: 41, or an N-terminal fragment of any preceding sequence that binds to a naturally occurring *patched* receptor.

24. **(Amended)** The method of claim 23, which polypeptide comprises an amino acid sequence designated in one of SEQ ID No: 8, SEQ ID No: 9, SEQ ID No: 10, SEQ ID No: 11, SEQ ID No: 12, SEQ ID No: 13, SEQ No: 14, SEQ ID No: 34, SEQ ID No: 40, SEQ ID No: 41, or an N-terminal fragment thereof that binds to a naturally occurring *patched* receptor.

25. **(Amended)** The method of claim 24, wherein said fragment comprises an extracellular fragment of at least 50 amino acids.

26. **(Amended)** The method of claim 23, wherein said neuronal cell phenotype is selected from motor neurons, cholinergic neurons, dopaminergic neurons, serotonergic neurons, and peptidergic neurons.

29. **(Amended)** A method for treating a degenerative disorder of the nervous system characterized by neuronal cell death, comprising administering to a patient an amount of a pharmaceutical preparation of a polypeptide including a *hedgehog* amino acid sequence at least 80% identical to an amino acid sequence designated in at least one of SEQ ID No: 8, SEQ ID No: 9, SEQ ID No: 10, SEQ ID No: 11, SEQ ID No: 12, SEQ ID No: 13, SEQ No: 14, SEQ ID No: 34, SEQ ID No: 40, SEQ ID No: 41, or an N-terminal fragment of any preceding sequence that binds to a naturally occurring *patched* receptor, thereby causing, relative to the absence of treatment, prolonged survival of neural cells in said patient, wherein said amount is effective to treat the degenerative disorder.

30. **(Thrice Amended)** The method of claim 29, wherein said *hedgehog* polypeptide comprises an amino acid sequence selected from SEQ ID No: 8, SEQ ID No: 9, SEQ ID No: 10, SEQ ID No: 12, SEQ ID No: 13, or SEQ ID No: 14, or an N-terminal fragment thereof that binds to a naturally occurring *patched* receptor.

31. **(Amended)** The method of claim 29, wherein said polypeptide comprises an amino acid designated in SEQ ID No. 41.

32. **(Amended)** The method of claim 29, wherein said polypeptide comprises an amino acid of SEQ ID No. 34 or an N-terminal fragment thereof that binds to a naturally occurring *patched* receptor.

33. **(Amended)** The method of claim 29, wherein said amount of the preparation inhibits the de-differentiation of neural cells of said patient.

34. **(Reiterated)** The method of claim 33, wherein said neural cell is a glial cell.

35. **(Reiterated)** The method of claim 33, wherein said neural cell is a nerve cell.

36. **(Reiterated)** The method of claim 29, wherein said degenerative disorder is a neuromuscular disorder.

37. **(Amended)** The method of claim 29, wherein said degenerative disorder is an autonomic disorder.

38. **(Reiterated)** The method of claim 29, wherein said degenerative disorder is a central nervous system disorder.

39. **(Amended)** The method of claim 29, wherein said degenerative disorder is selected from Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, Pick's disease, Huntington's disease, multiple sclerosis, neuronal damage resulting from anoxia-ischemia, neuronal damage resulting from trauma, and neuronal degeneration associated with a natural aging process.

40. **(Amended)** A method of claim 29, further comprising administering to said patient an amount of a growth factor having neurotrophic activity, wherein said growth factor enhances the effect of the treatment.

41. **(Amended)** The method of claim 40, wherein said growth factor is a nerve growth factor, ciliary neurotrophic growth factor, schwanoma-derived growth factor, glial growth factor, striatal-derived neuronotrophic factor, and platelet-derived growth factor.

Please add the following new claims:

42. (New) A method of claim 14, wherein the *hedgehog* amino acid sequence is at least 90% identical to an amino acid sequence designated in one of SEQ ID No: 8, SEQ ID No: 9, SEQ ID No: 10, SEQ ID No: 11, SEQ ID No: 12, SEQ ID No: 13, SEQ No: 14, or an N-terminal fragment of any preceding sequence that binds to a naturally occurring *patched* receptor.

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~~43.~~ (New) A method of claim 14, wherein the *hedgehog* amino acid sequence is at least 95% identical to an amino acid sequence designated in one of SEQ ID No: 8, SEQ ID No: 9, SEQ ID No: 10, SEQ ID No: 11, SEQ ID No: 12, SEQ ID No: 13, SEQ No: 14, or an N-terminal fragment of any preceding sequence that binds to a naturally occurring *patched* receptor.

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~~44.~~ (New) A method of claim 23, wherein the *hedgehog* amino acid sequence is at least 90% identical to an amino acid sequence designated in one of SEQ ID No: 8, SEQ ID No: 9, SEQ ID No: 10, SEQ ID No: 11, SEQ ID No: 12, SEQ ID No: 13, SEQ No: 14, or an N-terminal fragment of any preceding sequence that binds to a naturally occurring *patched* receptor.

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~~42.~~ (New) A method of claim 23, wherein the *hedgehog* amino acid sequence is at least 95% identical to an amino acid sequence designated in one of SEQ ID No: 8, SEQ ID No: 9, SEQ ID No: 10, SEQ ID No: 11, SEQ ID No: 12, SEQ ID No: 13, SEQ No: 14, or an N-terminal fragment of any preceding sequence that binds to a naturally occurring *patched* receptor.

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~~42.~~ (New) A method of claim 29, wherein the *hedgehog* amino acid sequence is at least 90% identical to an amino acid sequence designated in one of SEQ ID No: 8, SEQ ID No: 9, SEQ ID No: 10, SEQ ID No: 11, SEQ ID No: 12, SEQ ID No: 13, SEQ No: 14, or an N-terminal fragment of any preceding sequence that binds to a naturally occurring *patched* receptor.

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~~47.~~ (New) A method of claim 29, wherein the *hedgehog* amino acid sequence is at least 95% identical to an amino acid sequence designated in one of SEQ ID No: 8, SEQ ID No: 9, SEQ ID No: 10, SEQ ID No: 11, SEQ ID No: 12, SEQ ID No: 13, SEQ No: 14, or an N-terminal fragment of any preceding sequence that binds to a naturally occurring *patched* receptor.

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~~48.~~ (New) A method of claim 14, wherein the *hedgehog* amino acid sequence is at least 95% identical to an amino acid sequence designated in one of SEQ ID No: 40, SEQ ID No: 41, or an N-terminal fragment of any preceding sequence that binds to a naturally occurring *patched* receptor.

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~~49.~~ (New) A method of claim 14, wherein the *hedgehog* amino acid sequence is identical to an amino acid sequence designated in one of SEQ ID No: 40, SEQ ID No: 41, or an N-terminal fragment of any preceding sequence that binds to a naturally occurring *patched* receptor.

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~~50.~~ (New) A method of claim 23, wherein the *hedgehog* amino acid sequence is at least 95% identical to an amino acid sequence designated in one of SEQ ID No: 40, SEQ ID No: 41, or an N-terminal fragment of any preceding sequence that binds to a naturally occurring *patched* receptor.

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~~51.~~ (New) A method of claim 23, wherein the *hedgehog* amino acid sequence is identical to an amino acid sequence designated in one of SEQ ID No: 40, SEQ ID No: 41, or an N-terminal fragment of any preceding sequence that binds to a naturally occurring *patched* receptor.

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~~52.~~ (New) A method of claim 29, wherein the *hedgehog* amino acid sequence is at least 95% identical to an amino acid sequence designated in one of SEQ ID No: 40, SEQ ID No: 41, or an N-terminal fragment of any preceding sequence that binds to a naturally occurring *patched* receptor.

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~~53.~~ (New) A method of claim 29, wherein the *hedgehog* amino acid sequence is identical to an amino acid sequence designated in one of SEQ ID No: 40, SEQ ID No: 41, or an N-terminal fragment of any preceding sequence that binds to a naturally occurring *patched* receptor.

The claims presented above incorporate changes as indicated by the marked-up versions below.

1. **(Thrice Amended)** A method for promoting growth, differentiation, or survival of a cell comprising contacting said cell with an ~~effective~~ amount of a *hedgehog* polypeptide that binds to a naturally occurring *patched* receptor, which polypeptide is encoded by a nucleic acid that ~~which~~ hybridizes under stringent conditions, including a wash step of 0.2 x SSC at 65 °C or higher stringency, to a nucleic acid sequence selected from ~~the group consisting of~~ SEQ ID No:

1, SEQ ID No: 2, SEQ ID No: 3, SEQ ID No: 4, SEQ ID No: 5, SEQ ID No: 6 and SEQ ID No: 7, wherein said amount is effective to promote growth, differentiation, or survival of the cell.

2. **(Thrice Amended)** A method for promoting one or more of growth, differentiation, or survival of a mammalian cell responsive to *hedgehog* induction, comprising treating the cell with an ~~effective~~ amount of a *hedgehog* polypeptide that binds to a naturally occurring *patched* receptor, thereby altering, relative to the cell in the absence of *hedgehog* treatment, at least one of (i) rate of growth, (ii) differentiation, or (iii) survival of the cell, said *hedgehog* polypeptide being encoded by a nucleic acid that ~~which~~ hybridizes under stringent conditions, including a wash step of 0.2 x SSC at 65 °C or higher stringency, to a nucleic acid sequence selected from ~~the group consisting of~~ SEQ ID No: 1, SEQ ID No: 2, SEQ ID No: 3, SEQ ID No: 4, SEQ ID No: 5, SEQ ID No: 6 and SEQ ID No: 7, wherein said amount is effective to promote growth, differentiation, or survival of the cell.

5. **(Amended)** The method of claim 2, which polypeptide comprises an amino acid sequence designated in one of SEQ ID No: 8, SEQ ID No: 9, SEQ ID No: 10, SEQ ID No: 12, SEQ ID No: 13 or SEQ ID No: 14, or ~~a bioactive~~ an N-terminal fragment thereof that binds to a naturally occurring *patched* receptor.

6. **(Amended)** The method of claim 5, wherein said ~~bioactive~~ fragment comprises an extracellular fragment of at least 50 amino acids.

7. **(Amended)** The method of claim 2, which polypeptide comprises an amino acid sequence designated in SEQ ID No: 34, or ~~a bioactive~~ an N-terminal fragment thereof that binds to a naturally occurring *patched* receptor.

12. **(Amended)** The method of claim 11, which neuronal cells are selected from ~~the group consisting of~~ motor neurons, cholinergic neurons, dopaminergic neurons, serotonergic ~~serotonergic~~ neurons, and peptidergic neurons.

14. **(Amended)** A method for promoting, in an animal, cell growth, cell differentiation or cell survival, comprising administering ~~a therapeutically effective~~ an amount of a ~~*hedgehog*~~

polypeptide including a *hedgehog* amino acid sequence at least 80% identical to an amino acid sequence designated in one of SEQ ID No: 8, SEQ ID No: 9, SEQ ID No: 10, SEQ ID No: 11, SEQ ID No: 12, SEQ ID No: 13, SEQ No: 14, SEQ ID No: 34, SEQ ID No: 40, SEQ ID No: 41, or an N-terminal fragment of any preceding sequence that binds to a naturally occurring *patched* receptor, to alter, relative to the absence of ~~*hedgehog*~~ treatment, at least one of (i) rate of growth, (ii) differentiation, or (iii) survival of one or more cell[-] types in the animal, wherein said ~~hedgehog~~ polypeptide does not originate from drosophila, and wherein said amount is effective to promote cell growth, cell differentiation, or cell survival in the animal.

17. (**Amended**) A method of claim 14, which polypeptide comprises an amino acid sequence designated in one of SEQ ID No: 8, SEQ ID No: 9, SEQ ID No: 10, SEQ ID No: 11, SEQ ID No: 12, SEQ ID No: 13, SEQ No: 14, SEQ ID No: 34, SEQ ID No: 40, SEQ ID No: 41, or ~~a bioactive~~ an N-terminal fragment thereof that binds to a naturally occurring *patched* receptor.

18. (**Amended**) The method of claim 17, wherein said ~~bioactive~~ fragment comprises an extracellular fragment of at least 50 amino acids.

23. (**Amended**) A method for inducing a cell to differentiate to a neuronal cell phenotype, comprising contacting said cell with a ~~*hedgehog*~~ polypeptide including a *hedgehog* amino acid sequence at least 80% identical to an amino acid sequence designated in at least one of SEQ ID No: 8, SEQ ID No: 9, SEQ ID No: 10, SEQ ID No: 11, SEQ ID No: 12, SEQ ID No: 13, SEQ No: 14, SEQ ID No: 34, SEQ ID No: 40, SEQ ID No: 41, or an N-terminal fragment of any preceding sequence that binds to a naturally occurring *patched* receptor.

24. (**Amended**) The method of claim 23, which polypeptide comprises an amino acid sequence designated in one of SEQ ID No: 8, SEQ ID No: 9, SEQ ID No: 10, SEQ ID No: 11, SEQ ID No: 12, SEQ ID No: 13, SEQ No: 14, SEQ ID No: 34, SEQ ID No: 40, SEQ ID No: 41, or ~~a bioactive~~ an N-terminal fragment thereof that binds to a naturally occurring *patched* receptor.

25. (**Amended**) The method of claim 24, wherein said ~~bioactive~~ fragment comprises an extracellular fragment of at least 50 amino acids.

26. (**Am nded**) The method of claim 23, wherein said neuronal cell phenotype is selected from ~~the group consisting of~~ motor neurons, cholinergic neurons, dopaminergic neurons, serotonergic ~~serotenergic~~ neurons, and peptidergic neurons.

29. (**Amended**) A method for treating a degenerative disorder of the nervous system characterized by neuronal cell death, comprising administering to a patient ~~a therapeutically effective~~ an amount of a pharmaceutical preparation of a ~~*hedgehog*~~ polypeptide including a *hedgehog* amino acid sequence at least 80% identical to an amino acid sequence designated in at least one of SEQ ID No: 8, SEQ ID No: 9, SEQ ID No: 10, SEQ ID No: 11, SEQ ID No: 12, SEQ ID No: 13, SEQ No: 14, SEQ ID No: 34, SEQ ID No: 40, SEQ ID No: 41, or an N-terminal fragment of any preceding sequence that binds to a naturally occurring *patched* receptor, thereby causing, relative to the absence of ~~*hedgehog*~~ treatment, prolonged survival of neural cells in said patient, wherein said amount is effective to treat the degenerative disorder.

30. (**Thrice Amended**) The method of claim 29, wherein said *hedgehog* polypeptide comprises an amino acid sequence selected from ~~the group consisting of~~ SEQ ID No: 8, SEQ ID No: 9, SEQ ID No: 10, SEQ ID No: 12, SEQ ID No: 13, or SEQ ID No: 14, or ~~a bioactive~~ an N-terminal fragment thereof that binds to a naturally occurring *patched* receptor.

31. (**Amended**) The method of claim 29, wherein said ~~*hedgehog*~~ polypeptide comprises an amino acid designated in SEQ ID No. 41.

32. (**Amended**) The method of claim 29, wherein said ~~*hedgehog*~~ polypeptide comprises an amino acid of SEQ ID No. 34~~,~~ or ~~a bioactive~~ an N-terminal fragment thereof that binds to a naturally occurring *patched* receptor.

33. (**Amended**) The method of claim 29, wherein said ~~therapeutically effective~~ amount of the preparation ~~*hedgehog* polypeptide~~ inhibits the de-differentiation of neural cells of said patient.

37. (**Amended**) The method of claim 29, wherein said degenerative disorder is an autonomic disorder.